Technical Report: Acute Hepatitis of Unknown Cause

This is a technical report intended for scientific audiences. For additional information, including materials targeted to the general public, see Children with Acute Hepatitis of Unknown Cause.

Executive Summary

This report reviews what is currently known about acute hepatitis with unknown cause in children under the age of 11 years, and describes the investigations that CDC and state, local, tribal, and territorial partners are conducting.

As of June 22, 2022, 305 patients under investigation (PUIs) have been reported in 42 states and territories, with dates of onset on or after October 1, 2021. The median age of PUIs is 2 years. To date, 20 (6%) PUIs have required a liver transplant, and 11 (4%) have died; cause of death is under investigation. Since June 14, 15 additional PUIs were reported. However, only 7 PUIs experienced symptom onset between June 7–21, 2022.

Current patients under investigation (PUI) definition:

Children <10 years of age with elevated (>500 U/L) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) who have an unknown etiology for their hepatitis (with or without any adenovirus testing results, irrespective of the results) since October 1, 2021.

CDC is investigating several etiological hypotheses, notably a possible association with any adenovirus infection, and specifically type 41 infection. Of the 252 PUIs for whom adenovirus testing was conducted on any specimen type (blood, respiratory specimens, stool), 45% were found to be positive for adenovirus. Additional hypotheses, including a possible association with current or previous SARS-CoV-2 infection, or other viruses, are also being evaluated. Details on the leading hypotheses, planned investigations, and what is known to date are available below.

Clinical providers caring for children with hepatitis of unknown etiology should refer to the latest Guidance for Testing of Pediatric Patients Under Investigation and Guidance on Adenovirus Testing, Typing, and Testing Submission.

Disease Background

Hepatitis is inflammation of the liver. Its causes include viral infections, alcohol use, toxins, medications, and certain medical conditions. In the United States, the most common causes of viral hepatitis are hepatitis A, hepatitis B, and hepatitis C viruses.[2] Signs and symptoms of hepatitis include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, light-colored stools, joint pain, and jaundice.[2] Treatment of hepatitis depends on the underlying etiology.

Adenoviruses are doubled-stranded DNA viruses that spread by close personal contact, respiratory droplets, and fomites.[3] There are more than 50 types of immunologically distinct adenoviruses that can cause infections in humans. Adenoviruses most commonly cause respiratory illness, but some adenovirus types can cause other illnesses such as gastroenteritis, conjunctivitis, cystitis, and, less commonly, neurological disease.[3] There is no specific treatment for adenovirus infections.

Adenovirus type 41 commonly causes acute gastroenteritis in children, which typically presents as diarrhea, vomiting, and fever; it is often accompanied by respiratory symptoms.[4] While there have been case reports of hepatitis in immunocompromised children associated with adenovirus type 41 infection, adenovirus type 41 is not known to be a cause of hepatitis in otherwise healthy children.[5, 6]

Epidemiological Data by Geographic Area

Globally, the World Health Organization is reporting 650 probable cases from 33 countries in five WHO regions, with an additional 99 cases pending classification as of May 26, 2022. The majority of reported cases are from the WHO European Region (n=374), followed by the Region of the Americas (n=240), Western Pacific Region (n=34), the South-East Asia Region (n=14), and Eastern Mediterranean Region (n=5).

As of June 9, 2022, The European Centers for Disease Prevention and Control (ECDC) has received reports of 402 cases in 20 countries. Of the 192 cases for which this information was available, 17 (8.9%) have received a liver transplant. Overall, 293 cases were tested for adenovirus by any specimen type and had a valid positive or negative result. Of these, 158 (53.9%) tested positive. Of the 273 cases PCR tested for SARS-CoV-2, 29 (10.6%) tested positive. Additional information can be found on the ECDC surveillance bulletin .

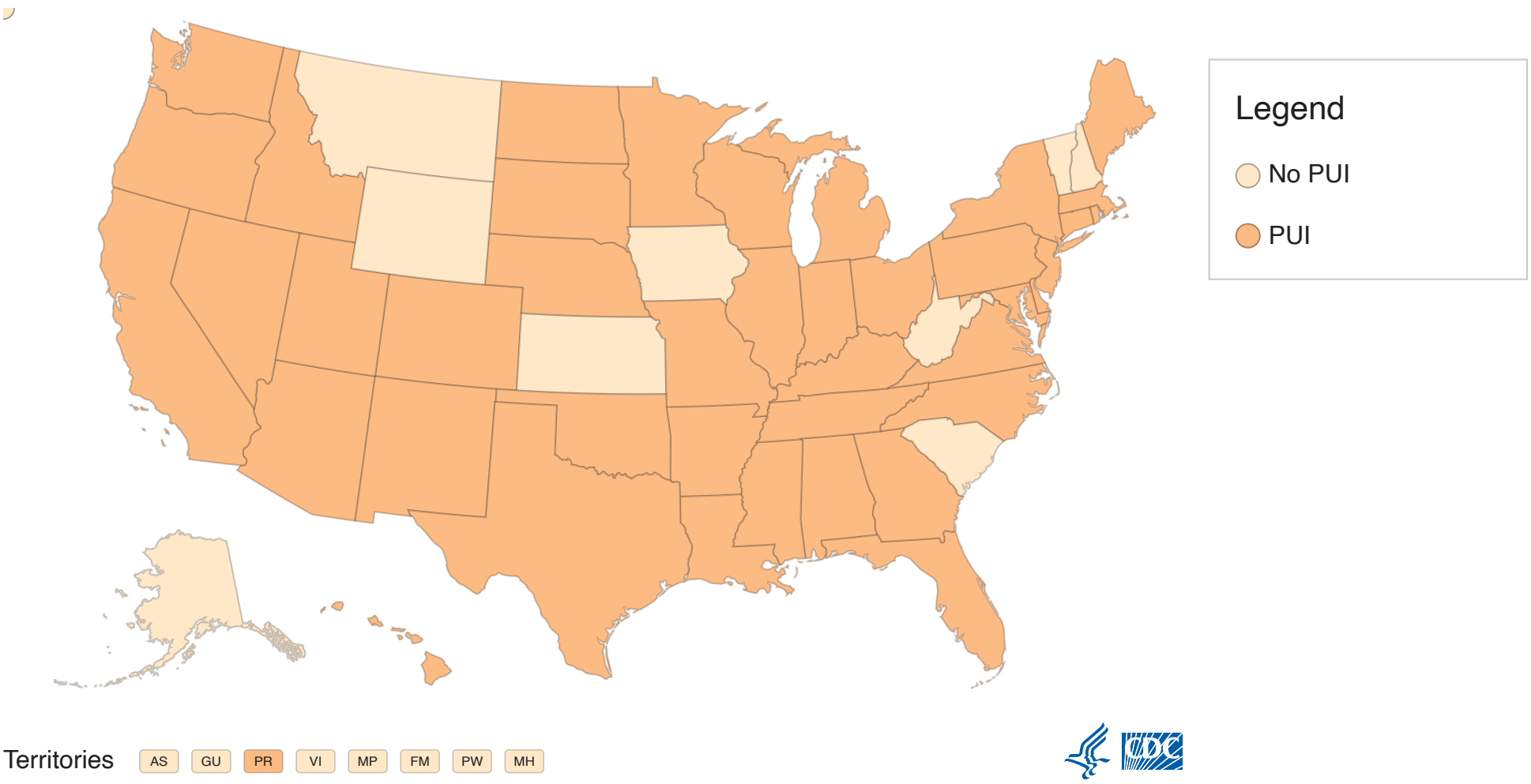
As of June 13, 2022, the United Kingdom is reporting 260 cases with onset dates between January 1, 2022, to present. Among 241 cases tested for adenovirus, 156 (65%) are positive. Of 196 PUIs tested for acute SARS-CoV-2 infection, 34 (17%) have tested positive. Additional data from the UK are available on the UKHSA briefing .

Summary Data of Patients Under Investigation in the United States

As of June 22, 2022, 305 patients under investigation (PUIs) have been reported from 42 jurisdictions. In the last week, 15 additional PUI have been reported. However, many of the newly reported PUIs had historical admissions that were identified retrospectively. The states reporting patients under investigation include: AL, AR, AZ, CA, CO, CT, DE, FL, GA, HI, ID, IL, IN, KY, LA, MA, MD, ME, MI, MN, MO, MS, NC, ND, NE, NJ, NM, NV, NY, OH, OK, OR, PA, PR, RI, SD, TN, TX, UT, VA, WA, and WI.

The median age of PUIs is 2 years (0–9 years), and 50% of PUIs are male.

Of the patients under investigation, 20 (7%) have required a liver transplant. Eleven deaths are under investigation.



Data Table

Location	Status
Alabama	PUI
Alaska	No PUI
American Samoa	No PUI

Location	Status
Arizona	PUI
Arkansas	PUI
California	PUI
Colorado	PUI
Connecticut	PUI
Delaware	PUI
District Of Columbia	No PUI
Florida	PUI
Georgia	PUI
Guam	No PUI
Hawaii	PUI
Idaho	PUI
Illinois	PUI
Indiana	PUI
Iowa	No PUI
Kansas	No PUI
Kentucky	PUI
Louisiana	PUI
Maine	PUI
Marshall Islands	No PUI
Maryland	PUI
Massachusetts	PUI
Michigan	PUI
Micronesia	No PUI
Minnesota	PUI
Mississippi	PUI
Missouri	PUI
Montana	No PUI
Nebraska	PUI
Nevada	PUI
New Hampshire	No PUI
New Jersey	PUI
New Mexico	PUI
New York	PUI
North Carolina	PUI
North Dakota	PUI
Northern Marianas	No PUI
Ohio	PUI
Oklahoma	PUI
Oregon	PUI
Palau	No PUI
Pennsylvania	PUI
Puerto Rico	PUI
Rhode Island	PUI

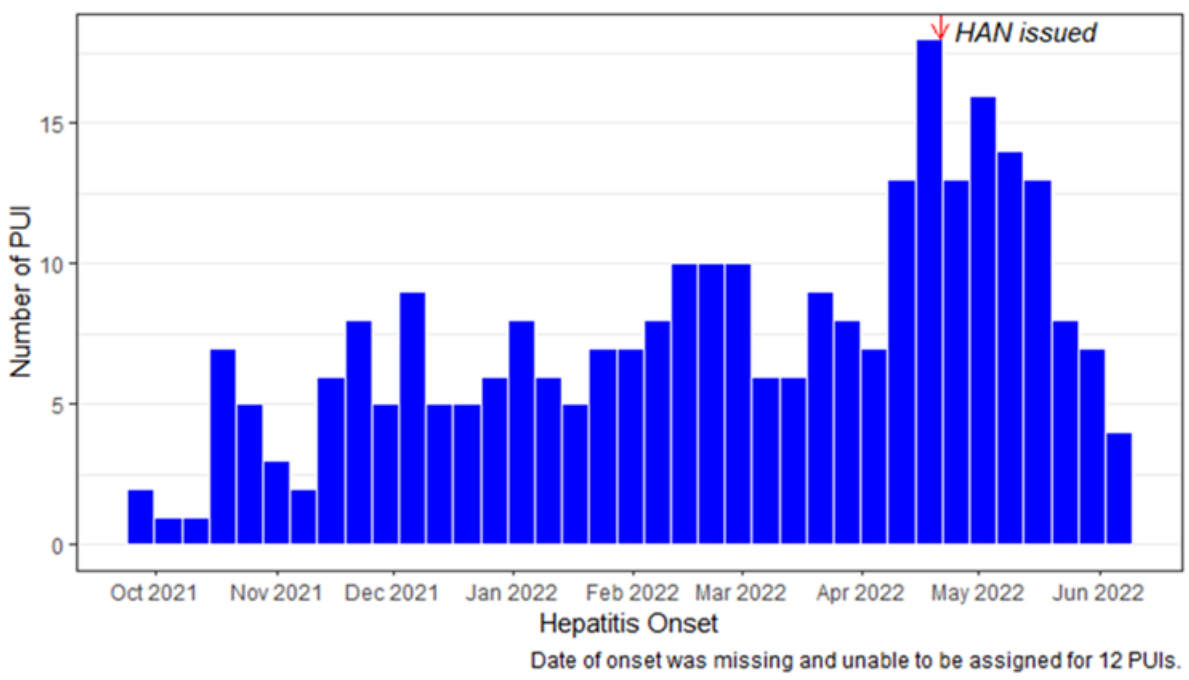
Location	Status
South Carolina	No PUI
South Dakota	PUI
Tennessee	PUI
Texas	PUI
Utah	PUI
Vermont	No PUI
Virgin Islands	No PUI
Virginia	PUI
Washington	PUI
West Virginia	No PUI
Wisconsin	PUI
Wyoming	No PUI

Download Data (CSV)

Source: https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/updates.html

Note: The number of PUIs and affected states/jurisdictions is updated weekly. Please use the website link for current information.

Reported patients under investigation with hepatitis of unknown etiology by week of onset October 2021–June 22, 2022 (n=295)



*Date of onset was missing and unable to be assigned for 10 PUIs

†A health advisory was issued via the CDC Health Alert Network on April 21, 2022

Of the 252 (83%) of PUIs with adenovirus testing on at least one specimen type (whole blood, plasma, serum, respiratory, stool), 45% were found to have adenovirus. Typing data is available for 20 PUIs; 13/20 were type 41, 1/20 was type 40, and 6 PUIs were other types (type 1(n=3), type 2(n=1), type 5 (n=1), type 6 (n=1)).

As reported in a recent MMWR, adenovirus was detected in the nine children with acute hepatitis initially reported in Alabama between October 2021 and February 2022.[1] High fidelity sequencing data for adenovirus typing was obtained for five patients, all of which were identified as adenovirus 41.

Hypotheses Under Investigation

CDC is investigating several etiologic hypotheses, notably a possible association with adenovirus infection, and specifically type 41 infection. Of the 252 patients under investigation for whom adenovirus testing was conducted on any specimen type (blood, respiratory, stool), 45% are positive for adenovirus. Ongoing and planned investigations include adenovirus testing, including typing and genome sequencing, for all PUIs with adequate specimens. This will facilitate understanding of the range of adenoviruses associated with acute hepatitis and if adenovirus is a previously unrecognized cause of pediatric hepatitis in non-immunocompromised children.

Selected additional etiologic possibilities include:

- **Do some children, due to age or other factors, exhibit an atypical response to their first adenovirus (or other viral) infection which results in hepatitis?** Pandemic mitigation measures have likely resulted in a large cohort of young children with minimal exposure to viral illnesses usually experienced in the first several years of life. Return to regular activities may have resulted in a larger than usual number of first infections, and at an older age than expected.
- **Are multiple factors contributing to the illnesses seen among reported PUIs, as opposed to one primary driver?** 30–50% [7-9] of liver failure in children is idiopathic; there are multiple known and unknown pathways to acute liver failure in children.
- **Is acute hepatitis in children due to a combination of persistent or prior infection with SARS-CoV-2 (or other viruses) and adenovirus, causing an autoimmune phenomenon or superantigen reaction?** Prevalence of an active SARS-CoV-2 infection is ~10% among PUIs for whom data is available, and up to 1/3 report history of prior COVID-19 infection. Testing for SARS-CoV-2 antibodies to confirm prior infections, as well as testing for viruses is ongoing.
- **Is acute hepatitis in children a manifestation of Multisystem Inflammatory Syndrome in Children (MIS-C), an inflammatory condition that develops in a small proportion of children after infection with SARS-CoV-2**? MIS-C associated with COVID-19 most often presents with cardiac or renal organ involvement, but occasionally signs of hepatitis. Among over 8,000 U.S. patients with MIS-C, <1% developed liver failure and nearly all were secondary to shock.
- **Is pediatric acute hepatitis caused by an environmental trigger or ingested toxin?** Although epidemiological investigations are still underway for the majority of PUIs, no associations have been found with pets, food, medication, toxins, or other exposures evaluated. However, this is analysis is preliminary and may change as additional information becomes available.

Trends in Surveillance Data

Analyses of four data sources did not indicate recent increases in hepatitis-associated ED visits or hospitalizations, liver transplants, or adenovirus 40/41 percent positivity among U.S. children compared with pre-COVID-19 pandemic levels. Additional analyses to establish baseline disease trends is presented in an MMWR publication.

- Trends in emergency department visits by children for acute hepatitis are largely stable for children birth through 4 years and 5 through 11 years of age based on National Syndromic Surveillance Program data from January 2018 to March 2022.
- Liver transplants among U.S. children aged <18 years do not demonstrate an increase since October 2021, compared with pre-pandemic levels in the Organ Procurement and Transplant Network.
- Hospitalizations consistent with acute hepatitis among children from birth to 4 years and 5–11 years do not demonstrate an increase since October 2021, compared with expected levels based on diagnostic codes in Premier Healthcare Database.
- Data from a large national commercial laboratory, by age birth to 4 years and 5–9 years, does not show an in increase in the percent positive for adenovirus 40/41 for 2021/2022 compared to 2019.

Investigations

Identifying the cause of acute hepatitis among children remains a high priority. CDC and partners are conducting extensive laboratory testing, including for adenovirus infection, and planning epidemiological and laboratory studies to examine the etiological hypotheses under investigation.

The following investigations are planned, ongoing or completed:

Category Category	Investigation Investigation	Partners Partners	Status Status
Epidemiological	Medical chart reviews and exposure histories of PUIs to identify most commonly shared possible etiologies and eliminate less likely causes	State, Local and Territorial (STLT) public health authorities	**Ongoing**. Based on preliminary analysis, adenovirus is detected in approximately 50% of PUIs tested, and SARS-CoV-2 infection was detected in approximately 10% of PUIs with a PCR or antigen test. Publication of a PUI case series is planned for late June 2022.
	Trends in pediatric hepatitis utilizing ICD-10-CM codes from emergency department (ED) visits, hospitalizations, as well as organ transplant databases (2018-present) to establish if current cases exceed expected cases	CDC in collaboration with partners – National Syndromic Surveillance Program (NSSP), the Premier Healthcare Database (PHD-SR), and the Organ Procurement and Transplant Network (OPTN)	**Completed**. No increases in pediatric hospitalizations, ED visits, or liver transplants detected (MMWR).
	Prospective case-control study of ED/hospitalized patients to assess risk factors for acute hepatitis	CDC and STLT public health authorities	**Ongoing**. Protocol finalized and shared with jurisdictions for implementation consideration. Based on current case accrual, investigators anticipate sufficient number of cases and controls may be enrolled by October 2022 for analysis.
Clinical	Clinical case series to describe the characteristics of a group of acute hepatitis cases, all of whom had adenovirus	CDC, STLT public health authorities	**Completed**. In-depth clinical case series review of the initial Alabama cases completed (data publicly available in MMWR) and additional PUIs in upcoming publication.
	Host susceptibility studies (e.g., HLA typing, PBMC/CD analysis) to assess possible etiologic factors	Under discussion (between CDC and partners)	**Planned**. In partnership with government and academic centers.
Surveillance	Detection of human adenovirus (HAdV) 41 from stool testing to assess trends in number of tests and percent positivity	CDC, Labcorp	**Completed**. Data do not show an increase above pre-pandemic levels in the percent positive for adenovirus 40/41 from October 2021 through March 2022 compared to similar months in 2017–2019 (MMWR).
	Review MIS-C case surveillance data for trends in acute hepatitis over the past 2 years	CDC	**Ongoing**. Analysis of MIS-C surveillance data to examine patterns of hepatic involvement following SARS-CoV-2 infection over time to look for increased hepatic involvement after October 2021.

Category	Investigation	Partners	Status
Microbiological	Adenovirus diagnostic testing and typing of clinical specimens for PUIs	CDC (in collaboration with partners)	**Ongoing**. As of June 22, 2022, 252 (83%) of PUIs have had adenovirus testing completed on at least one specimen type. Of those tested, 45% are positive for adenovirus. 11/16 PUIs with typing results are type 40/41.
	Detection of prior SARS-CoV-2 infections	STLT public health authorities and CDC	**Ongoing**. Recommendation made for testing SARS-CoV-2 antibodies as part of the evaluation of PUIs. Retrospective serologic testing of available specimens ongoing.
	Metagenomics and whole genome sequencing of HAdV41 to understand pathogen variants and virulence factors, and detection of potential coinfections	CDC (in collaboration with partners)	**Ongoing**. Phylogenetic analysis of detected adenovirus strains. Testing of initial acute hepatitis cluster completed and will proceed for additional PUIs. Initial testing confirms presence of Adenovirus, type 41, as well as presence of Adeno-associated viruses (AAV) type 2.
	Detection of Adenovirus in fecal specimens from children with acute gastroenteritis to serve as controls without hepatitis.	CDC and New Vaccine Surveillance Network (NVSN)	**Planned**. Retrospective testing of specimens for AdV type 41 from a sentinel hospital active surveillance network for acute gastroenteritis in children across seven sites. Testing anticipated to begin in July 2022.
Pathology	Pathology assessment of biopsy and explant liver tissue, and autopsy to investigate mechanism of liver injury	CDC and clinical institutions (as part of routine care)	**Ongoing**. As of June 22, 2022, CDC's Infectious Diseases Pathology Branch has received liver tissue specimens from 23 PUIs. Of 6 PUIs for which initial findings have been described (MMWR), liver demonstrated varying degrees of acute hepatitis, changes are non-specific but not typical for adenovirus hepatitis, with no viral inclusions observed and negative immunohistochemistry, electron microscopy.

Partnerships

CDC is hosting weekly calls with state, tribal, local, and territorial partners to coordinate the investigations and response. In addition, CDC is working with groups representing clinical specialists from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), Infectious Disease Society of America; American Association for the Study of Liver Disease; the Pediatric Infectious Diseases Society; and American Academy of Pediatrics to produce diagnosis and management guidance for clinicians caring for patients with acute hepatitis of unknown cause. More information can be found on the NASPGHAN website . Clinical guidance for testing, posted on the CDC clinician portal: Clinical Guidance for Adenovirus Testing and Typing of Patients Under Investigation.

CDC is partnering with colleagues at state, local, tribal and territorial health departments, as well as clinical and laboratory experts, to conduct investigations to evaluate the leading etiological hypotheses. Further, the CDC is in close communication with colleagues in the United Kingdom, Israel, CDC, and regional/international health organizations (e.g., ECDC, PAHO, and WHO) to exchange data and findings.

Risk Assessment (based on time of publication)

At this time, the incidence of acute hepatitis in children is not higher than pre-pandemic baseline levels, and severe outcomes are infrequent. Investigations are ongoing to better understand cases of acute hepatitis of unknown etiology in children. CDC encourages parents and caregivers to be aware of the symptoms of hepatitis—particularly jaundice, which is a yellowing of the skin or eyes—and to contact their child's healthcare provider if present.

Limitations of the Report

Adenoviruses are very common in humans and typically cause only mild illness. Few surveillance systems exist in the United States to detect adenovirus infections or distinguish it from the other pathogens that cause mild upper respiratory or gastrointestinal disease. CDC has leveraged existing data sources to define the burden of hepatitis and evaluate secular trends. Hepatitis Emergency Department and hospitalization data are based on discharge diagnosis codes that have not been extensively validated. All data are preliminary and may change as more reports are received.

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Authors and Contributors are members of the CDC Acute Hepatitis of Unknown Cause Response.

References

See All References

1. Baker JM. Acute Hepatitis and Adenovirus Infection Among Children—Alabama, October 2021–February 2022. MMWR. Morbidity and Mortality Weekly Report. 2022;71.
2. Hepatitis Webpage. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/hepatitis/abc/index.htm
3. Adenoviruses Webpage. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/adenovirus/index.html
4. Kang G. Viral Diarrhea. International Encyclopedia of Public Health [Internet]. Elsevier; 2017. P. 260-7. Available from https://www.sciencedirect.com/science/article/pii/B9780128036785004860 .
5. Munoz RE, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children . Clinical Infectious Diseases. 1998 Nov 1;27(5):1194-200. doi: 10.1086/514978
6. Peled N, Nakar C, Huberman H, Scherf E, Samra Z, Finkelstein Y, et al. Adenovirus Infection in Hospitalized Immunocompetent Children . Clin Pediatr (Phila). 2004 Apr;43(3):223–9.
7. Squires RH Jr, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group . J Pediatr 2006;148:652–8
8. Alonso EM, Horslen SP, Behrens EM, et al. Pediatric acute liver failure of undetermined cause: a research workshop . Hepatology 2017;65:1026–37
9. Squires JE, Alonso EM, Ibrahim SH, Kasper V, Kehar M, Martinez M, Squires RH. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure. Journal of Pediatric Gastroenterology and Nutrition . 2022 Jan 9;74(1):138-58.

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